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Single C−F Transformations of *o*-Hydrosilyl Benzotrifluorides with Trityl Compounds as All-in-One Reagents

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Cite This: https://dx.doi.org/10.1021/acs.orglett.0c03529 Read Online

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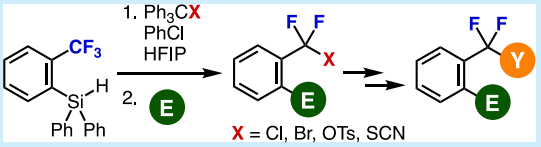
ABSTRACT: A facile method to prepare difluoromethylenes, including α,α-difluorobenzyl chlorides, by single C−F transformations of benzotrifluorides is disclosed. The C−F cleavage followed by chlorination proceeded smoothly using trityl chloride through the generation of trityl cation as an activator and chloride anion as a nucleophile. Diverse difluoromethylenes such as difluorobenzyl ethers were efficiently prepared by virtue of the good versatility of the resulting chloro and fluorosilyl groups.



Organofluorines are of great significance in a broad range of disciplines such as materials chemistry, pharmaceutical sciences, and chemical biology.[1] In particular, difluoromethylenes are attractive as bioactive compounds and organic materials because of the properties affected by the introduction of fluorine atoms.[2−8] In spite of continuous efforts to develop synthetic methods for difluoromethylenes, synthesizing a broad range of difluoromethylenes is still challenging because of the limitation of available building blocks and transformations.[2−8] Herein we disclose a practical method for preparing α,α-difluorobenzyl chlorides as versatile organofluorine building blocks. This facile synthesis was achieved by single C−F chlorination of *o*-hydrosilyl benzotrifluorides with trityl chloride as an all-in-one reagent for generating trityl cation as an activator and chloride anion as a nucleophile.

In contrast to benzyl halides as fundamental building blocks in synthetic organic chemistry, transformations of α,α-difluorobenzyl halides are still limited because of their poor accessibility (Figure 1).[8] Pioneering works by Yoshida and coworkers in the 1990s showed potentially versatile transformability of α,α-difluorobenzyl chlorides as electrophiles and α,α-difluorobenzyl radical precursors, but the synthesis of α,α-difluorobenzyl chlorides from arenes and bis(chlorodifluoroacetyl) peroxide was not easy (Figure 1A).[8a] In 2020, Young and coworkers reported that single C−F functionalization of benzotrifluorides could be achieved using a frustrated Lewis pair from 2,4,6-triphenylpyridine and a catalytic amount of tris(pentafluorophenyl)boron and following treatment with nucleophiles, including chloride anion (Figure 1B).[6] We independently accomplished single C−F transformations of benzotrifluorides assisted by activation of an *o*-hydrosilyl group with a trityl cation in the presence of nucleophiles such as allylsilanes.[7a] We also achieved the synthesis of an *o*-fluorosilyl-substituted α,α-difluorobenzyl chloride in moderate yield by treating an *o*-hydrosilyl benzotrifluoride with trityl tetrafluoroborate and a diethyl ether solution of hydrochloric acid.[7a] Recently, C−F thiolation

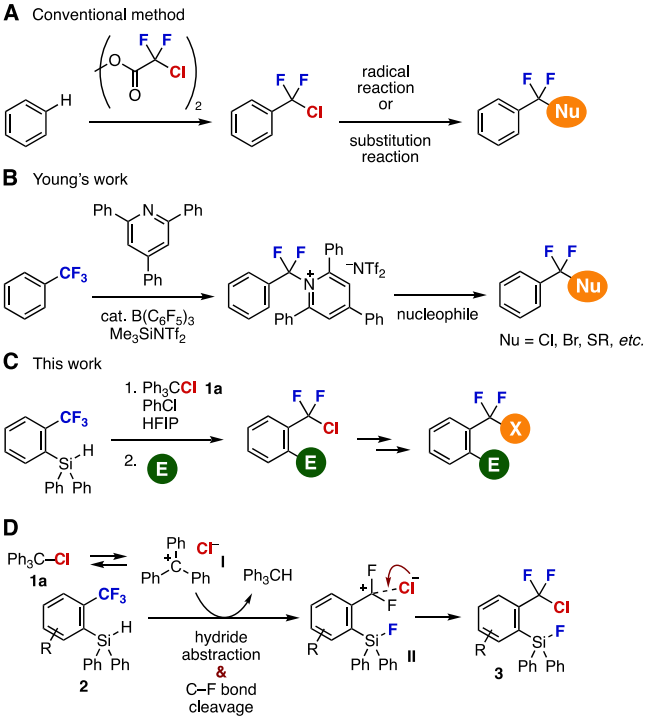


Figure 1. Background and plan of this study. (A) Conventional methods. (B) Young's work. (C) This work. (D) Working hypothesis of this study.

Received: October 23, 2020

https://dx.doi.org/10.1021/acs.orglett.0c03529
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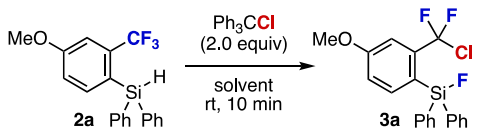
of *o*-hydrosilyl benzotrifluorides was achieved using trityl sulfides as all-in-one reagents to generate a trityl cation and thiolate anions activated by ytterbium catalysis.[7b] Considering the higher stability of chloride anion compared with thiolates,[9] we envisioned that C−F chlorination of *o*-hydrosilyl benzotrifluorides would take place with trityl chloride (**1a**) through equilibrium generation of trityl cation and chloride anion without any Lewis acid catalysis (Figure 1C).[10] The generation of trityl cation and chloride anion would trigger hydride abstraction from benzotrifluoride **2** and fluoride migration followed by nucleophilic attack of chloride anion to difluorobenzyl cation **II** to provide difluorobenzyl chloride **3** (Figure 1D). Since the resulting chloro and fluorosilyl groups can be transformed to various functional groups, a wide range of difluoromethylenes can be synthesized from difluorobenzyl chlorides **3**.

As expected, C−F chlorination of *o*-hydrosilyl benzotrifluoride **2a** with trityl chloride proceeded without any Lewis acid catalysis (Table 1).[11] We found that the desired *o*-

Table 1. Optimization of the Reaction Conditions



entry	solvent	yield (%)[a]
1	CH_2Cl_2/HFIP (1:1 v/v)	88
2	CH_2Cl_2/HFIP (19:1 v/v)	83
3	CH_2Cl_2/HFIP (49:1 v/v)	62
4	CH_2Cl_2	0
5	HFIP	50
6	DMSO	0
7	DMF	0
8	CH_3NO_2	0
9	CH_2Cl_2/TFE (1:1)	10
10	PhCl/HFIP (1:1)	quant. (90[b])

[a]Yields based on ^{1}H NMR analysis. [b]The isolated yield for the reaction conducted on a 3.0 mmol scale is shown in parentheses.

fluorosilyl-substituted difluorobenzyl chloride **3a** was obtained in good yield when benzotrifluoride **2a** was treated with trityl chloride dissolved in dichloromethane and 1,1,1,3,3,3-hexafluoro-2-propanol (HFIP)[12] (1:1 v/v) and that further C−F transformations of **3a** did not occur (entry 1). Decreasing the amount of HFIP to 5 or 2 vol % slightly reduced the yield of **3a** (entries 2 and 3). On the other hand, no reaction proceeded in the reaction without HFIP, similar to our previous reports (entry 4).[7] In addition, difluorobenzyl chloride **3a** was prepared in moderate yield when HFIP was solely used as a solvent (entry 5). Difluorobenzyl chloride **3a** was not obtained when other polar solvents such as DMSO, DMF, and nitromethane were used (entries 6−8). Furthermore, 2,2,2-trifluoroethanol (TFE) instead of HFIP slightly facilitated C−F chlorination (entry 9). Chlorobenzene instead of dichloromethane improved the efficiency (entry 10). The good scalability was demonstrated by a gram-scale synthesis of **3a** in high yield.

A broad range of fluorosilyl-substituted difluoromethylenes **3b−j** were successfully prepared by C−F functionalizations with trityl compounds (Figure 2A). For example, difluorobenzyl chlorides **3b−e** were prepared from benzotrifluorides

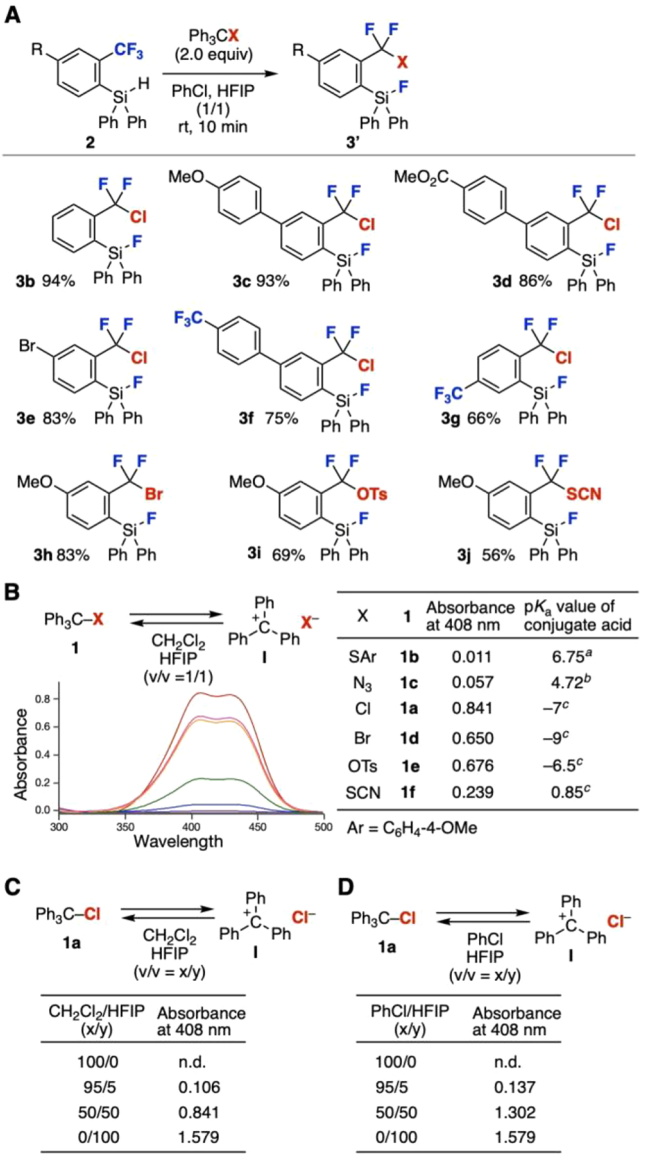


Figure 2. C−F transformations using trityl compounds. (A) Scope of C−F transformations using trityl compounds. (B) Absorption spectra of trityl compounds **1** in CH_2Cl_2/HFIP (1:1 v/v) at 50 μM (red line, X = Cl; pink line, X = OTs; orange line, X = Br; green line, X = SCN; blue line, X = N_3; purple line, X = SAr). (C) Absorbance at 408 nm in CH_2Cl_2/HFIP (100:0 to 0:100 v/v) at 50 μM. (D) Absorbance at 408 nm in PhCl/HFIP (100:0 to 0:100 v/v) at 50 μM. [a]Data from ref 9a. [b]Data from ref 9b. [c]Data from ref 9c.

in high yields without damaging methoxy, methoxycarbonyl, and bromo groups. The yield of defluorochlorination product **3b** was significantly improved from our previous result using trityl tetrafluoroborate and hydrochloric acid.[7a,13] It is noteworthy that the selective C−F chlorination afforded difluorobenzyl chlorides **3f** and **3g** having an unreacted trifluoromethyl group in good yields. Not only chlorination but also bromination, tosyloxylation, and thiocyanation proceeded smoothly without any Lewis acid catalysis.[14] It is noteworthy that various transformations from C−F to C−Cl, C−Br, C−OTs, and C−SCN were achieved by this simple procedure using only trityl compounds.

The generation of trityl cation from trityl compounds **1a** and **1d−f** was confirmed by absorption spectra in dichloromethane

https://dx.doi.org/10.1021/acs.orglett.0c03529
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and HFIP, while a small concentration of trityl cation was generated from trityl thiolate **1b** or trityl azide **1c** (Figure 2B). The cleavabilities of trityl compounds to generate trityl cation and the corresponding counteranions were attributed to the stability of the counteranions, which were clearly shown by pK_a values of the conjugate acids.[9] The concentration of trityl cation was increased by increasing the amount of HFIP, and trityl cation was not detected when only dichloromethane or chlorobenzene was used (Figure 2C,D).

Various *ortho*-functionalized difluorobenzyl chlorides were synthesized by transformations of the fluorosilyl group (Figure 3A). Indeed, we succeeded in the synthesis of difluorobenzyl chlorides **4**–**8** by protonation with wet tetrabutylammonium fluoride, arylation by palladium-catalyzed Hiyama cross-coupling with aryl iodide,[15] and halogenations with *N*-halosuccimides.[16] These results clearly show that the single defluorochlorination of the trifluoromethyl group and subsequent C–Si transformations based on the good reactivity of the fluorosilyl group can be used to prepare a broad range of *ortho*-substituted difluorobenzyl chlorides.

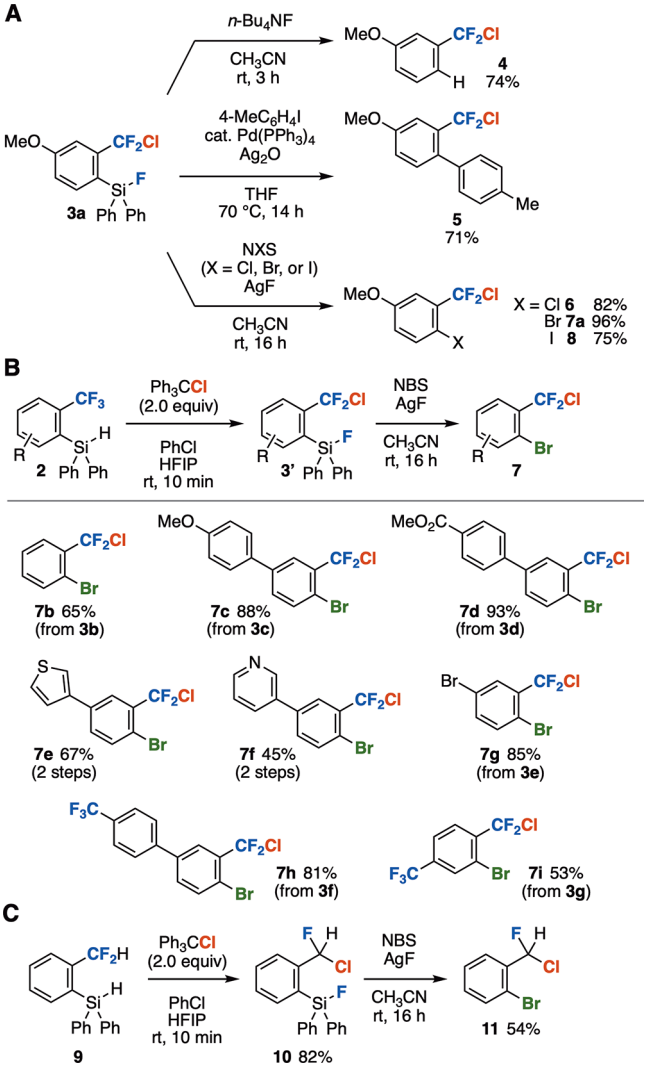

Figure 3. C–F chlorination and C–Si transformations. (A) C–Si transformations of **3a**. (B) Synthesis of *o*-bromo-substituted difluorobenzyl chlorides **7**. (C) C–F chlorination and C–Si bromination of **9**.

The C–F chlorination and C–Si bromination sequence enabled us to prepare a wide variety of *o*-bromo-substituted difluorobenzyl chlorides (Figure 3B). For example, not only *o*-bromo-α,α-difluorobenzyl chloride (**7b**) but also 4-anisyl- and 4-(methoxycarbonyl)phenyl-substituted difluorobenzyl chlorides **7c** and **7d** were efficiently prepared from **3b**–**d**, respectively. We also synthesized heteroaromatic-substituted difluorobenzyl chlorides **7e** and **7f** by C–F chlorination and C–Si bromination of *o*-hydrosilyl-substituted benzotrifluorides in two steps. Electron-deficient 2,5-dibromo-α,α-difluorobenzyl chloride (**7g**) was successfully prepared in good yield. It is noteworthy that we accomplished the synthesis of difluorobenzyl chlorides **7h** and **7i** bearing a trifluoromethyl group keeping the difluoromethylene group intact. These results clearly indicated an advantage of this study since the facile synthesis of α,α-difluorobenzyl chlorides having a transformable *o*-bromo group was a challenging issue in the previous C–F transformations.[5,6] Additionally, the preparation of α-fluorobenzyl chloride **11** was also achieved via C–F chlorination of the difluoromethyl group of **9** and subsequent C–Si bromination (Figure 3C).[5c,17]

The good transformability of the chloro group enabled the synthesis of a wide range of difluorobenzyl ethers from alcohols under basic conditions (Figure 4A). Such ethers are difficult to prepare by conventional methods because of the

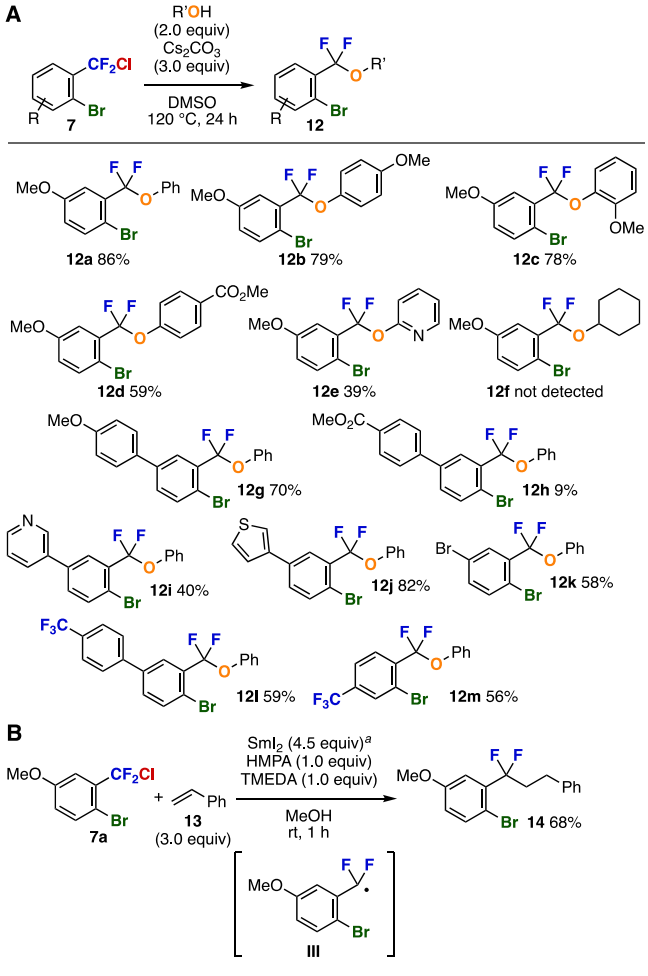

Figure 4. Transformations of the chloro group. (A) Synthesis of various difluorobenzyl ethers **12**. (B) Radical addition using **7a**. [a]SmI_2 was added in two portions. See the Supporting Information for details.

https://dx.doi.org/10.1021/acs.orglett.0c03529
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limited accessibility of difluorobenzyl chlorides.[8h] Indeed, heating difluorobenzyl chloride **7a** possessing a bulky bromo group at the *ortho* position with phenol in the presence of cesium carbonate in DMSO furnished difluorobenzyl ether **12a** in high yield, and no side product formed by C−F cleavage was observed.[18] Difluorobenzyl ethers **12b** and **12c** were also prepared from 4- and 2-methoxyphenol, respectively. We also succeeded in the synthesis of difluorobenzyl ether **12d** in moderate yield leaving the ester moiety untouched. It is noteworthy that *O*-benzylation proceeded selectively to provide **12e** when difluorobenzyl chloride **7a** was treated with 2-pyridone, and the *N*-benzylation product was not detected. Unfortunately, cyclohexyl difluorobenzyl ether **12f** was not detected in the reaction of **7a** with cyclohexanol. Furthermore, various difluorobenzyl chlorides participated in the difluorobenzyl ether synthesis. For instance, 4-methoxyphenyl-substituted difluorobenzyl ether **12g** was efficiently synthesized by *O*-benzylation of phenol. In addition, methoxycarbonyl-substituted difluorobenzyl ether **12h** was prepared, albeit in low yield. *O*-Benzylation of phenol allowed for the preparation of difluorobenzyl ethers **12i** and **12j** possessing heteroaromatic rings. We also accomplished the synthesis of electron-deficient difluorobenzyl ethers **12k−m** having bromo- and trifluoromethyl groups. The difluorobenzyl ether synthesis would be useful in pharmaceutical sciences and agrochemistry since a broad range of benzyl ethers are bioactive compounds and replacing hydrogen atoms with fluorines has gained attention as a means to modulate the properties such as bioactivity, lipophilicity, and stability toward oxidation.

Samarium-mediated reductive radical addition between difluorobenzyl chloride **7a** and styrene (**13**) realized further C−C bond formation through difluorobenzyl radical **III** (Figure 4B). Indeed, treatment of **7a** and **13** with samarium iodide in the presence of HMPA and TMEDA in methanol afforded difluoromethylene **14** in good yield without C−F cleavage or damage to the bromo group.[8d] Thus, the significant versatility of difluorobenzyl chlorides allowed us to synthesize a wide range of organofluorines by not only substitution reactions but also radical reactions.

In summary, we have developed an efficient method for the synthesis of α,α-difluorobenzyl chlorides through single C−F chlorination of benzotrifluorides with trityl chloride assisted by an *o*-hydrosilyl group. Equilibrium generation of trityl cation and chloride anion from trityl chloride facilitated the efficient C−F chlorination leaving the difluoromethylene group intact, whereas it is not easy to prepare difluoromethylenes by previously reported defluorohalogenation methods.[10] The good transformabilities of the chloro and fluorosilyl groups realized the synthesis of diverse difluorobenzyl ethers having a transformable *o*-bromo group. Further studies to expand synthesizable organofluorines involving the development of synthetic methods for *o*-hydrosilyl-substituted benzotrifluorides are ongoing in our group.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.0c03529.

Experimental procedures and characterization data for new compounds, including NMR spectra (PDF)

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

The authors thank Dr. Yuki Sakata at Tokyo Medical and Dental University for HRMS analyses. This work was supported by JSPS KAKENHI Grants JP19K05451 (C; S.Y.), JP18H02104 (B; T.H.), and JP18H04386 (Middle Molecular Strategy; T.H.); the Naito Foundation (S.Y.); the Japan Agency for Medical Research and Development (AMED) under Grant JP20am0101098 (Platform Project for Supporting Drug Discovery and Life Science Research, BINDS); the Cooperative Research Project of the Research Center for Biomedical Engineering; and the Research Program of "Five-Star Alliance" in "Network Joint Research Center for Materials and Devices". HRMS analyses were performed using research equipment shared in MEXT Project for Promoting Public Utilization of Advanced Research Infrastructure (Program for Supporting Introduction of the New Sharing System), Grant JPMXS0422300120.

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